page 4, lines 23-26; page 6, lines 9-15; page 12, lines 21-23; page 13, lines 16-20; page 21, lines 28-30; page 33, line 6 through page 37, line 21; page 71, line 26 through page 72, line 28; page 73, line 1 through page 74, line 6; in Figures 4 and 5, and in the Sequence Listing. No new subject matter has been added. For the Examiner's convenience, attached hereto is an Appendix containing the currently pending claims in this application, including the new claims added by the Amendment submitted herewith.

An Advisory Action was mailed by the Patent and Trademark Office (hereinafter "PTO") on October 17, 2002, asserting that the rejections of claims under 35 U.S.C. §112, first paragraph, have been overcome. The Advisory Action asserted, however, that the rejection under 35 U.S.C. §102(b) was maintained "because the scope of Applicant's claims is not limited to SEQ ID NOS:1,5,9,11 and 13 but to polynucleotides which hybridize, therefore the antibodies of record would bind." Applicants thank the Examiner for a brief, clarifying telephonic interview on November 14, 2002, in which the Examiner asserted that deletion of part (c) from claim 94 "would remove all rejections of record."

Applicants also gratefully acknowledge an opportunity to further discuss the present application, along with clarifying comments provided by the Examiner, in a second telephonic interview on January 15, 2003. In particular, the Examiner confirmed that the amendment submitted by Applicants on September 20, 2002, which was an amendment only to the specification, has been entered on the record.

REJECTION UNDER 35 U.S.C. §102(B)

Claims 94-103 stand rejected under 35 U.S.C. § 102(b) for allegedly being unpatentable over U.S. Patent 5,453,492 ('492) as evidenced by Bost et al., and Bendayan as evidenced by Hay et al., and Harlow et al. Specifically, the PTO concedes that '492 is silent with respect to the amino acid sequence of the TGF-beta-1 binding protein described therein, and with respect to any nucleotide sequence encoding such protein. The PTO asserts, however, that a polypeptide having a sequence encoded by the polynucleotide recited in part (c) of instant claim 94 is inherently disclosed as the TGF-beta-1 binding protein in '492, where the TGF-beta-1 binding protein of '492 and the polypeptide recited in part (c) are allegedly obtained from the same source. The PTO asserts that absent any showing by Applicants that the polypeptide

recited in part (c) is not the same as the TGF-beta-1 binding protein of '492, antibodies that are encompassed by claim 94 allegedly must include antibodies that bind to the TGF-beta-1 binding protein as disclosed in '492.

Applicants respectfully traverse these grounds for rejection. For reasons previously made of record, the PTO has failed to establish a *prima facie* case of anticipation under 35 U.S.C. §102(b) because no evidence or reasoning has been presented by the PTO to show that antibodies which bind to the TGF-beta-1 binding protein of '492 include any antibodies which specifically bind to a TGF-beta binding protein according to the present invention (see, *e.g.*, instant specification at page 6, lines 9-11; page 33, lines 8-11), nor has the PTO proffered any extrinsic evidence to show that the TGF-beta-1 binding protein of '492 must *necessarily* be encoded by a polynucleotide as recited in part (c) of claim 94.

Furthermore, and again for reasons previously made of record, Applicants submit that the PTO errs in asserting that Applicants have the burden of supplying extrinsic evidence to supplement the incomplete disclosure of '492, where the PTO can at most allege that the antibodies disclosed in '492 "might" recognize TGF-beta binding proteins disclosed in the present application.

Applicants respectfully submit that the art well knows that both the TGF-beta protein superfamily, and the distinct family of TGF-beta binding proteins, are extensive and highly varied, such that absent any showing to the contrary by the PTO, there would be no reason for a person skilled in the art to believe that antibodies that bind to the TGF-beta-1 binding protein according to '492 would necessarily also bind to a TGF-beta binding protein according to the presently claimed invention. For the Examiner's convenience, Applicants are enclosing a copy of Balemans et al. (2002 *Dev. Biol.* 250:231), an exemplary recent review article which is not prior art but which summarizes the diversity in structures, cell and tissue origins, and binding specificities of binding proteins that interact with one or more members of the highly diverse TGF-beta superfamily (see, *e.g.*, Balemans et al. at pp. 235-244, including disclosure pertaining to "sclerostin", an alternative nomenclature used for the "Beer" proteins described in the present application). In the present specification (*e.g.*, page 12, lines 21-23; page 13, lines 16-20; page 33, lines 8-11; and elsewhere) the subject matter encompassed by the instant claims is satisfactorily described, as the PTO has previously conceded, and Applicants

respectfully submit that the skilled artisan would have no basis for concluding that the presently claimed subject matter is *necessarily* coextensive in scope with any antibody disclosed in '492. Accordingly, the PTO has failed to meet its burden of establishing that the subject matter of the presently claimed invention is inherently present in '492.

M.P.E.P §2112 provides that:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) (emphasis in original).

Accordingly, Applicants submit that the burden remains with the PTO to supply the requisite basis in fact and/or technical reasoning, where, as Applicants have previously argued, mere conjecture on the part of the PTO does not suffice as a finding that the prior art reference contains a disclosure that anticipates the presently claimed invention. Furthermore, the PTO has offered no evidence making clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (*Continental Can Co. USA v. Monsanto Co.*,948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (M.P.E.P. § 2131.01 (III)).

In the telephonic interview of January 15, 2003, the Examiner asserted that M.P.E.P. §2112.02, which cites *In re Spada* (911 F.2d 705, 709; 15 USPQ2d 1655, 1658, Fed. Cir. 1990), provides the basis for Applicants' having to assume the burden of presenting evidence to show that the claimed invention is not inherently present in the cited '492 patent.

Applicants respectfully traverse this assertion and submit that *In re Spada* is misapplied to the present application. In *Spada,* a product was claimed that had an identical chemical composition to a product that was described, *in terms of its chemical composition*, in a cited prior art reference; certain properties of the composition were claimed as unanticipated. The facts in *Spada* can be distinguished from the instant application because, *inter alia*, the '492 patent presently cited by the PTO fails to provide the detailed chemical composition (*i.e.*, amino acid sequence or polynucleotide coding sequence) of the TGF-beta-1 binding protein described therein. Thus, the PTO falls short of providing any "sound basis for believing that the products

of the prior art and the applicant are the same", which is required, according to *Spada*, before any burden shifts to the applicant to show they are not (*Id.*)

In other words, in *Spada,* no extrinsic evidence was required to show that the prior product and the claimed product had identical chemical compositions. The '492 patent, by contrast, fails to disclose the TGF-beta-1 binding protein structure (*i.e.*, its chemical composition, such as the amino acid sequence), without which it cannot be determined whether the presently claimed antibody could possibly have been inherently present. Moreover, unlike the '492 patent cited by the PTO in the instant application, the prior art reference cited in *Spada* included every limitation recited in the claims. It is axiomatic that for a cited reference to anticipate a claimed invention, each and every limitation of the claim must be present in a single reference. Applicants therefore submit that the PTO has failed to meet its burden of supplying extrinsic evidence to supplement the incomplete disclosure of '492, and that the PTO therefore cannot demonstrate that an antibody of '492 *necessarily* must bind to a TGF-beta binding protein as recited according to the instant claims. Accordingly, no *prima facie* case of anticipation under 35 U.S.C. §102(b) has been established, and Applicants respectfully request that the rejection be withdrawn.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Mary E. Brunkow et al.

SEED Intellectual Property Law Group PLLC

Stephen J. Rosenman, Ph.D.
Registration No. 43,058

SJR:kw

Enclosures:
Copy of Balemans et al., 2002 *Dev. Biol.* 250:231-250

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

APPENDIX—CURRENTLY PENDING CLAIMS

94. An isolated antibody or binding fragment thereof which binds to a TGF-beta binding protein, wherein said binding protein is selected from the group consisting of:

(a) an isolated polypeptide encoded by a polynucleotide sequence selected from SEQ ID NOs:1, 5, 9, 11, 13, and 15, or complementary sequences thereof;

(b) an isolated polypeptide selected from SEQ ID NOs: 2, 6, 10, 12, 14, and 16; and

(c) an isolated polypeptide encoded by a polynucleotide that specifically hybridizes to a polynucleotide encoding the polypeptides of (a) under conditions of high stringency, wherein high stringency conditions are prewashing in 60 mM Tris pH 8.0, 2 mM EDTA, 5x Denhardt's, 6x SSC, 0.1% (w/v) N-laurylsarcosine, 0.5% (w/v) NP-40 (nonidet P-40) overnight at 45°C, followed by two washes with 0.2x SSC containing 0.1% SDS at 45-50°C.

95. The isolated antibody or binding fragment thereof of claim 94, wherein the isolated antibody or binding fragment thereof is a polyclonal antibody.

96. The isolated antibody or binding fragment thereof of claim 94, wherein the isolated anti body or binding fragment thereof is a monoclonal antibody.

97. The isolated antibody or binding fragment thereof of claim 94, wherein the isolated antibody or binding fragment thereof is a humanized antibody.

98. The isolated antibody or binding fragment thereof of any one of claims 94-97, wherein the antibody has an affinity of at least 10^{-7}M.

99. The isolated antibody or binding fragment thereof of any one of claims 94-97, wherein the antibody has an affinity of at least 10^{-8}M.

100. A hybridoma that produces an antibody according to any one of claims 94-97.

101. A method of producing monoclonal antibodies, comprising:

(a) immunizing an animal with a TGF-beta binding protein or portion thereof;

(b) harvesting spleen cells from said animal;

(c) fusing said spleen cells with a myeloma cell line; and

(d) culturing said fused cells under conditions that allow the production of said antibody.

102. A method for the production of an antibody of any one of claims 94-97 comprising culturing hybridoma cells under conditions that allow the production of said antibody.

103. A method for the production of an antibody of any one of claims 94-97 comprising:

(a) providing a recombinant host cell capable of producing said antibody; and

(b) culturing said cell under conditions that allow the production of said antibody.

104. (New) An isolated antibody or binding fragment thereof which binds to a TGF-beta binding protein, wherein said binding protein is selected from the group consisting of:

(a) a polypeptide encoded by a polynucleotide that comprises a nucleotide sequence selected from SEQ ID NOs:1, 5, 9, 11, 13, and 15, or a complementary sequence thereto, and

(b) a polypeptide that comprises an amino acid sequence selected from SEQ ID NOs: 2, 6, 10, 12, 14, and 16.

105. (New) An isolated antibody or binding fragment thereof which binds to a TGF-beta binding protein, wherein said binding protein is selected from the group consisting of:

(a) a polypeptide encoded by a polynucleotide that comprises a nucleotide sequence selected from SEQ ID NOs:1, 5, 9, 11, 13, and 15, or a complementary sequence thereto;

(b) a polypeptide that comprises an amino acid sequence selected from SEQ ID NOs: 2, 6, 10, 12, 14, and 16; and

(c) a polypeptide encoded by a polynucleotide having at least 90% identity with a full length sequence selected from SEQ ID NOs:1, 5, 9, 11, 13, and 15, or a complementary sequence thereto.

106. (New) The antibody of claim 105 wherein the polypeptide of (c) specifically binds to at least a human bone morphongenic protein selected from the group consisting of bone morphogenic protein 5 and bone morphogenic protein 6.

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